UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/572,882	10/10/2006	Stefan Golz	2004P56028 WOUS	5299

28524 7590 10/02/2009

SIEMENS CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
170 WOOD AVENUE SOUTH
ISELIN, NJ 08830

EXAMINER	
LIU, SAMUEL W	

ART UNIT	PAPER NUMBER
1656	

MAIL DATE	DELIVERY MODE
10/02/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/572,882	GOLZ ET AL.	
	Examiner	Art Unit	
	SAMUEL LIU	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/27/07, 7/13/09 & 9/29/09*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *2,3 and 12-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 4-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *3/20/06* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20060320*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Attached "Notice to comply"*.

DETAILED ACTION

Status of claims

Claims 1-26 are pending.

The preliminary amendment filed 3/20/06 which amends claims 1-12 and 18-26 has been entered. The applicants' request filed 7/13/09 for extension of time of three months has been entered.

Foreign Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Germany on 9/27/03 under 35 U.S.C. 119(a-d) and 119(e).

IDS

The references cited in the IDS filed 3/20/06 have been considered by Examiner.

Election/Restrictions

Applicants' election filed 7/13/09 of Group I, claims 1 and 4-11 without traverse is acknowledged. Based on the interview on 7/28/09, and upon communication with applicants' representative Noam R. Pollack on 9/29/09, Applicants' additional election of cardiovascular disease for examination has been confirmed. Claims 2, 3 and 12-26 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 1 and 4-11 and the elected "cardiovascular disease" are under examination.

Objection to specification

The disclosure is objected to because of the following informalities:

(1) The continue data of this application needs to be updated.

(2) At page 1, line 9, "AdipoR2" should be spelled out in full for the first instance of use. Similarly, see also page 97, line 15, "DNAase".

(3) The specification is objected to because of trade-name ""Cytosensor™" (page 45, line 31), ""BIAcore™" (page 46, line 10), and "Cremophor EM™" (page 79, line 26). It should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

(4) At page 95, line 27, "SEQ ID NO 753" should be changed to "SEQ ID NO:753"; similar changes should be made throughout the specification.

Sequence compliance

This application contains sequences disclosures at pages 95-97, i.e., "SEQ ID NO 753 (p.95, line 27), SEQ ID NO 968, SEQ ID NO2936 and SEQ ID NO 1690 (p.96, lines 5, 15 and 20, respectively), and SEQ ID NO 2603 (p.97, line 5), that are encompassed by the definitions for amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). Note that the "Sequence listing" of instant application contains only SEQ ID NOs: 1-5 but not those SEQ ID NOs mentioned above. Thus, this application fails to comply with one or more of the requirements of 37 C.F.R. § 1.821 through 1.825 for one or more of the reasons set forth on the attached form "Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequences And/Or Amino Acid Sequence Disclosures". Wherein attention is directed to paragraph(s) §1.82 (c) and (e). Although an examination of this application on the merits can proceed without prior compliance, compliance with the Sequence Rules is required for the response to this Office action to be complete.

* Note that the attached PTO "*Notice to comply*" is applied only to the above-mentioned SEQ ID NOs, but not applied to instant SEQ ID NOs:1-5 filed 3/20/06.

Objection to claims

Claims 1 and 4-11 are objected to because of containing non-elected subject matters, i.e., "dermatological diseases, gastroenterological diseases, cancer, hematological diseases, respiratory diseases, inflammation, neurological diseases and urological diseases".

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 1 and 4-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The method of Claim 1 appears to be incomplete because of lack of step of assaying for whether or not the "binding" detected in step (ii) has effect on modulating bioactivity of the AdipoR2 polypeptide which is G protein coupled receptor [GPCR] (see p.1, line 18, the specification). In has been known in the relative art that the GPCR possesses non-productive binding mode (see abstract, Hulme et al. (1995) *Life Sci*. 56, 891-898), i.e., a compound capable of binding to a GPCR, however, does not result in productive outcome, e.g., modulating biological activity of said GPCR protein; one of examples of this is that binding of a mutant G protein α_s subunit to its receptor gives rise to non-productive outcome (see p.36604, right col., last paragraph, Cleator et al. (2004) *J. Biol. Chem*., 279, 36601-36607). Thus, claim 1 should include the step as to determining whether the binding of step (ii) would result in modulatory

effect of test compound on AdipoR2 receptor. Claims 4-11 which depend from claim 1 are also rejected.

Claim 4 does not make it clear whether or not "a cell" which membrane comprises the AdipoR2 polypeptide; or/and whether or not "a cell" is obtained from a patient who has been diagnosed to have a "CVD".

Claim 8 recitation "coupled to" is unclear whether or not it refers to that the polypeptide function is associated (coupled) with an action of "dateable label", or refers to that the polypeptide is structurally (e.g., covalently) linked with said label. (Please see "G protein ***coupled*** receptor" set forth at page 1, line 18, the specification, wherein the "*coupled*" is not a structural linkage).

Claim 9 recites "the test compound displaces a ligand which is first bound to the polypeptide"; the recitation is not apparent whether or not the "displaces" does not actually occur but rather refers to a theoretical mechanism of ligand binding. Suggest "the test compound displaces a ligand which has bound to the polypeptide in said binding set forth in claim 1".

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

- *Scope of enablement*

Claims 1 and 4-11 are rejected under 35 U.S.C. 112, first paragraph, because while the specification may enable a screening method of using a full-length AdipoR2 polypeptide to

screen/identify a certain type(s) of "cardiovascular disease" (a large genus encompassing a large number of disease states or conditions associated with atherosclerosis, myocardial infarction, arrhythmic death, stroke and vascular rupture and see details below) wherein pathologies of said certain type of cardiovascular disease has been known at time instant invention was made, does not reasonably provide enablement for using a ferment or/and a variant AdipoR2 polypeptide, or using peptide or oligopeptide thereof to screen/identify a therapeutic compound for treating *any* cardiovascular diseases/conditions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546(BPAI 1986). They include the nature of the invention, the state of the art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

(1) The scope of the claims/(2)The nature of the invention:

Claim 1 and claims dependent from are directed to a method of screening a compound capable of treating "a cardiovascular disease" (CVD) using "a AdipoR2 polypeptide"; wherein, in absence of the sequence identifier(s), the phrase "a AdipoR2 polypeptide" is considered to encompass any portions (fragments), or/and mutants (variants) [substitution, deletion and/or insertion] of the full-length AdipoR2 polypeptide comprising SEQ ID NO:2 (see Fig. 2, p.5, line 20, the specification).The specification neither teaches the amino acid sequences of said

fragments or/and variants nor teaches the common structure(s)/sequence(s) [i.e., core or consensus domain(s)] critical for maintaining the therapeutic function of the AdipoR2 polypeptide relative to treating the "CVD". The specification fails to provide working example of use of the fragments or/and the variants in screening for the CVD drug.

In order to screen a therapeutic compound (drug) capable of treating the "CVD" state, said "CVD" disease state should have characterized pathology due to the following reasons.

The "CVD" is a lager genus encompassing various diseases and conditions from all diseases/conditions related to vascular system, like congestive heart failure, myocardial infarction, ischemic diseases of the heart, all kinds of arterial and ventricular arrhythmias, hypertensive vascular diseases, peripheral vascular diseases to atherosclerosis; and, even encompasses conditions/disease states relative to atherosclerosis and coronary artery or carotid artery disease including disorders of lipid metabolism, e.g., hyperlipidemia, obesity, hereditary hyperlipidemia, types II-V hyperlipoproteinemias, hypolipoproteinemia, lipidoses, Gaucher's disease, Niemarm-Pick disease, Fabry's disease, Wolman's disease, cerebrotendinous xanthomatosis, sitosterolemia, Refsum's disease, and Tay-Sachs disease (pages 55-58, the specification). Of them, some "CVD" such as Tay-Sachs disease is untreatable (see Dr. Spock (2009, updated) "*Screening for Tay-Sachs disease*" www.drspock.com/article /0,1510,6257,00.html, pages 1 and 2). Said "untreatable" would render screening the drug that is used for treating the untreatable disease inoperable. Moreover, clinical diagnosis of a cardiovascular disease is frequently inaccurate (p.6, right col., 3rd paragraph, Maas et al. (2003) *Atheroscler. Suppl.*, 4, 5-17), suggesting that the "CVD" state which is prerequisite for said drug screening needs to be pathologically identified/characterized prior to performing said screening.

One skilled in the art thus would have had to unduly search for proper "CVD" states before he or she is able to conduct the screening method. In this case, therefore, the scope of the claims is outside the realm of routine experimentation.

(3) The unpredictability of the art:

The relative art teaches that, in a large part of the literature, the term "cardiovascular disease" is imprecise and has been used to describe rather imprecisely defined array of different conditions, and teaches that there are confusion in evaluation of "cardiovascular disease" (p. 6, left col., 3rd paragraph, lines 1-7 and 13-16, Maas et al.). Clinical diagnosis of a cardiovascular disease is frequently inaccurate (p.6, right col., 3rd paragraph, Maas et al.). Said "imprecise", "confusion" and "inaccurate" render the screening useful therapeutic compound for treating a "CVD" unpredictable.

The acute cardiovascular disease such as stroke is unpredictable (page IV-33, left col., last paragraph, lines 8-10, Cohn et al. (2004) *Circulation*, 109, IV31-46). If the "CVD" per se cannot be properly diagnosed, then, the results of screening compound for said "CVD" must not be predictable. Therefore, the level of the unpredictability of the art is very high.

(4) The state of the art:

There are confusion, imprecision and discrepancy in teaching the "CDV" states (see Maas et al. reference above). The art also teaches that the mechanisms involved in the "CVD" are too diverse as to be useful in more than handful of patients, and teaches that the pathogenesis of cardiovascular disease is multifunctional in most patients (p. 13, right col., 2nd paragraph, lines 6-12, Maas et al.). None of Examples 1-14 in the specification provides using the AdipoR2 polypeptide or the variant/fragment thereof to screen the therapeutic compound capable of

treating the "CVD" state. While Example 10 discusses drug screening in general, instant disclosure is silent in teaching screening for any particular "CVD" state using the AdpoR2 polypeptide or fragment/variant thereof. Considering the above-discussed diversity and multi-functionality due to the CVD clinical mechanisms or modes, the specification needs to provide sufficient guidance to be considered enabling for the claimed screening method.

(5) The quantity of experimentation necessary:

In the absence of working examples with regard to the genus stated above, unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trials and errors to practice the claimed invention. The amount of experimentation to screening and identifying the therapeutic compound for treating a characterized or diagnosed "CVD" state using the AdipoR2 polypeptide including the fragment and the variant thereof (see above) is NOT routine and enormous. One skilled in the art would require additional guidance in this regard in order to feasibly screen/identify said therapeutic compound. Without such guidance, the experimentation left to those skilled in the art is undue.

(6) The relative skill of those in the art:

The general knowledge and level of skill in the art do not supplement the omitted description with respect to the promoter and the host discussed above. In view of the preceding factors (1-5), the level of skill in this art is high and requires at least an oncologist, with several years of experience in drug screening, cardiology and medicinal fields relative to the "cardiovascular disease" and pharmacology as well as knowledge in protein engineering and pathology. Yet, even with a level of skill in the art as those mentioned in precedence, predictability of the results is still highly variable.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view of the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention. Thus, the amount and level of experimentation needed is undue.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Rejection under 35 U.S.C 102(e), Patent Application Publication or Patent to Another with Earlier Filing Date, in view of the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 4-10 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) over as obvious over Wu et al. (US Pat. 7435808 B2).

Wu et al. teach a method of using AdipoR2 polypeptide for drug screening comprising competitive binding assay for a test therapeutic compound (col. 196, lines 32-55). Wu et al. teach that AdipoR2 has ability of stimulating vascular endothelial cell growth useful for treating the CVD such as arteriosclerosis (see col.207, lines 48-53, and col. 177, line 14 to col.179, lines 10). The binding assay comprising step of combining the test compound with a host cell expressing the AdipoR2 polypeptide, and step of measuring (detecting) an effect of the compound on the activity of the AdipoR2 receptor protein (see col. 10, lines 8-57). These teach claims 1 and 4.

Wu et al. teach use of immobilized AdipoR2 polypeptide in the binding assay wherein said polypeptide is immobilized on a cell surface or solid support (col. 196, lines 47-49, col. 197, lines 11-15, and Example 12), which teaches claims 5, 6 and 10.

Sine, in the competitive binding assay, an AdipoR2 ligand must have bound to the AdipoR2 receptor polypeptide prior to the test compound displace said ligand, claim 9 is inherently rejected.

In the binding assay, the polypeptide is detectably labeled (col.193, lines 53-55 and lines 61-64), which teaches claim 7.

Claim 8 as written is indefinite (see above) wherein the term "coupled to" is broadly but reasonably interpreted as either functionally "coupled to" or structurally linked to a detectable label (see "*G protein **coupled** receptor*" set forth at page 1, line 18, the specification, wherein the "*coupled*" is NOT a structural linkage). Wu et al. teach that the "competitive binding assay" involves a competition between the test compound and a labeled competitor (col. 193, lines 21-26); here, the compound is considered to be "coupled" to the label of said competitor in term of the competitive binding to the AdipoR2 receptor polypeptide. Thus, clam 8 is inherently rejected.

Claim Rejections - 35 USC §103

The text of the sections of 35 USC 103(a) not included in this section can be found above.

[1] Claims 1 and 4-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamauchi et al. (Nature (June 2003) 423, 762-769, from the IDS) in view of Kadowaki et al. (US 204/0241802 A1, Yamauchi is a coauthor of this reference).

Yamauchi et al. teach use of the cloned AdipoR2 polypeptide in understanding (obvious variation of detecting/screening for) cardiovascular disease such as atherosclerosis (see p.768, left col., last paragraph), as applied to claim 1.

Yet, Yamauchi et al. do not expressly teach actual steps of the screening.

Kadowaki et al. teach a screening method and screening kit for said method (see [0203], lines 6 and 7, and patent claim 8), and teach amino acid sequence of AdipoR2 polypeptide (named "protein [**a**]", see [0036]). Further, Kadowaki et al. teach the method comprises steps of contacting test compound (ligand, agonist or antagonist) with "protein [**a**]", i.e., AdipoR2 protein, and step of determining whether or not the compound binds to the AdipoR2 protein and affects activity of the AdipoR2 receptor protein (see [0100]), as applied to claim 1.

The test compound is labeled (see [-104]), as applied to claim 8.

The screening kit is used for in vitro screening assay, this inherently teaches claim 6.

The screening kit comprises a "transformant" (i.e., host cell transformed with expression vector encoding AdipoR2 DNA, e.g., mouse SEQ ID NO:7) (see patent claims 1-3 and 8, and [0110]). This suggests that the screening uses the host cell *in vitro* which cell membrane contain AdipoR2 receptor, as applied to claims 4 and 5.

In the binding assay, the detectably labeled human AdipoR2 polypeptide is used (see [0137], [0154] and Fig. 5), as applied to claim 7.

The competitive binding assay is used (see [0181] and Fig. 5) for the binding assay in order to screen the test compound. Sine in the competitive binding assay, an AdipoR2 ligand must have bound to the AdipoR2 receptor polypeptide prior to the test compound displace said ligand, the above Kadowaki teaching is inherently applied to claim 9.

Because the trans-membrane feature is an inherent property of AdipoR2 receptor (G protein coupled receptor, see page 1, line 18, the specification), and because the screening kit (used for the screening assay) contains the host cell (see above), the cell membrane in which

AdipoR2 protein resides is considered to be equivalent to instant "solid support", claim 10 is rejected.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to develop the screening method for identifying the therapeutic compound capable of treating a known cardiovascular disease such as atherosclerosis. This is because Yamauchi et al. have taught that AdipoR2 receptor protein likely involves in development of cardiovascular disease, e.g., atherosclerosis and relative disorder thereof, e.g., diabetes (p.768, left col., last paragraph). It is of note that diabetes is within scope of "CVD" in accordance with the specification teaching at page 57, line 27.

Kadowaki et al. have taught that adiponectin (peptide hormone), which is a native ligand for the AdipoR2 receptor, is a vital insulin sensitizing hormone, and that hypertrophy of lipid cell, which secrete adiponectin, decreases adiponectin hormone excretion and thereby leads to insulin resistance, which in turn is a cause of diabetes and hyperlipidemia disorders (see [0107]). Also, Kadowaki et al. have taught that the agonist or antagonist compounds (i.e., test compound) of the adiponectin receptor (i.e., AdipoR2 protein) are subjected to the screening so as to discover drug for treating said disorders (see [0107], lines 6-12, and [0108], lines 1-3, 15 and 16). The Kadowaki's teachings suggest usefulness of the AdipoR2 receptor protein in screening drugs for treating diabetes and atherosclerosis (caused by hyperlipidemia). In view of the reference teaching as to the involvement of AdipoR2 in development of cardiovascular disease (Yamauchi et al.), and further, in view of the teaching with regard to (the method steps) how to perform the screening (see [0100], Kadowaki), one of ordinary skill in the art would have realized feasibility of the AdioR2 polypeptide in screening/identifying the therapeutic "CVD"

compound for treating disease such as atherosclerosis, and thus, would have been motivated to try screening for said compound. When tried, it would have necessarily led to reasonable expectation of success. Therefore, combination of the references' teachings would have rendered the claimed method *prima facie* obvious.

[2] Claims 1 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamauchi et al. (Nature (June 2003) 423, 762-769, from the IDS) in view of Kadowaki et al. (US 204/0241802 A1) as applied to claim 1, and further in view of Schreiber et al. (US 2002/0173474 A1).

The teachings of claim 1 by Yamauchi et al. and Kadowaki at al. have been set forth above.

Yamauchi et al. and Kadowaki et al. do not expressly teach that the compound is immobilized on a solid support for the screening.

At [0058], lines 22-27, Schreiber et al. teach that, in the screening method, the compound capable of binding to a receptor (note the instant AdioR2 is a G protein coupled receptor) can be identified (detected) by direct or competitive binding assay wherein said compound is immobilized on solid support, as applied to claim 11.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to immobilize the compound, which is subjected to the screening, on a solid support in the direct or competitive binding assay. This is because the immobilization of the compound is an obvious alternative way of immobilization of the receptor (that binds the compound and the receptor ligand) and is well within the purview of one of ordinary skill in the art. The compounds

capable of binding the receptor protein can be routinely identified by various methods including the above-discussed binding assay; in one of these methods, the compound is immobilized as taught by Schreiber et al. (see [0058], lines 22-27). Thus, one of ordinary skill in the art would have tried said immobilization in said screening method according to Kadowaki et al. with reasonable expectation of success. Therefore, combination of the references' teachings renders claim 11 *prima facie* obvious in the absence of unexpected result.

[3] Claims 1 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu et al. (US Pat. 7435808 B2) as applied to claim 1, and further in view of Yu et al. (US 2003/0083261A1).

The teaching of claim 1 by Wu at al. has been set forth above.

Wu et al. do not expressly teach that the compound is detectably labeled.

Yu et al. teach that, in a competitive binding assay for screening a test compound, either the compound or the protein (target) capable binding of said compound can be labeled for determining of binding (see [0097], lines 9-14), as applied to claim 8.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to label the test compound in said assay. This is because labeling the compound is an obvious variation of an alternative of labeling the AdipoR2 receptor to which the compound binds, and becasue Yu et al. have taught that either the compound or the receptor protein can be labeled for the competitive binding assay. It is of note that both Wu and Yu teach the same assay, i.e., the competitive binding assay, and teach use of said assay to accomplish the screening. Thus, one of ordinary skill in the art would have tried labeling the compound with reasonable

expectation of success. Therefore, combination of the references' teachings renders claim 11 *prima facie* obvious in the absence of unexpected result.

[4] Claims 1 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu et al. (US Pat. 7435808 B2) as applied to claim 1, and further in view of Schreiber et al. (US 2002/0173474 A1).

The teaching of claim 1 by Wu at al. has been set forth above.

Wu et al. do not expressly teach that the compound is immobilized on a solid support for the screening assay.

Schreiber et al. teach that, in screening method, the compound capable of binding to a receptor (note the instant AdioR2 is a G protein coupled receptor) can be identified (detected) by direct or competitive binding assay wherein said compound is immobilized on solid support, as applied to claim 11.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to immobilize the compound subjected to the screening on a solid support in the direct or competitive binding assay. This is because the immobilization of the compound is an obvious alternative way of immobilization of the receptor that binds the compound and ligand of said receptor as well as well within the purview of one of ordinary skill in the art. The compounds binding to the receptor protein can be identified by various methods including the above-discussed binding assay wherein the compound is immobilized as taught by Schreiber et al. (see [0058], lines 2-27). Thus, one of ordinary skill in the art would have tried said immobilization in

the screening method with reasonable expectation of success. Therefore, combination of the references' teachings renders claim 11 *prima facie* obvious in the absence of unexpected result.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Liu whose telephone number is (571)272-0949. The examiner can normally be reached on Monday-Friday, 9 am to 5:30 pro.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Samuel Wei Liu/
Patent Examiner, Art Unit 1656
/ANAND U DESAI/
Primary Examiner, Art Unit 1656
September 30, 2009